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Three Minute, But Not One Minute, Ischemia and Nicorandil Have a Preconditioning Effect in Patients With Coronary Artery Disease

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OBJECTIVES This study focused on 1) the determination of the optimal preconditioning (PC) duration, and 2) the protective effect of nicorandil (NC), a hybrid nitrate with a KATP channel opening effect, during a percutaneous transluminal coronary angioplasty (PTCA) model in humans.

BACKGROUND The ischemic PC effect is induced in 180 s ischemia, but not in 120 s ischemia in rabbit hearts. However, the duration of ischemia that induces PC effect and the role of the KATP channel in the PC effect in humans are still unclear.

METHODS Forty-six patients with stable angina were randomly allocated to four groups: the duration of the first inflation as PC ischemia was 60 s in the PC60 group (n = 12), and 180 s in the PC180 group (n = 12). In the other groups, NC (80 μg/kg) was intravenously given for 1 min in the NC group (n = 12), and isosorbide dinitrate (ISDN) (40 μg/kg) was given in the ISDN group (n = 10). Five minutes after first inflation or drug administration, a second inflation was conducted for 120 s in each group. In the ECG, the lead with the largest shift in ST segment (deltaST max), and the sum of elevated ST levels in all leads (sigmaST) were determined.

RESULTS In the PC60 group, no significant difference was observed in either deltaST max or sigmaST between the first and second inflation. However, the second inflation in the PC180 group showed significantly lower levels of deltaST max and sigmaST compared with those of the first inflation. In the NC group, both deltaST max and sigmaST measured at 30 s and 60 s after balloon inflation were significantly lower than those of the first inflation in the PC60 and PC180 control groups. In the ISDN group, no significant difference was observed in deltaST max or sigmaST.

CONCLUSION In human PTCA models, a PC effect is observed in 180 s ischemia, but not in 60 s ischemia. A pharmacological PC effect is induced by NC, a KATP channel opener with a nitrate-like effect but not ISDN. This suggests that the opening of KATP channels plays an important role in the protecting effect of NC. (J Am Coll Cardiol 2000;35:345–51) © 2000 by the American College of Cardiology

In animal experimental models such as dogs, pigs, rabbits and rats, brief episodes of ischemia and reperfusion precondition the myocardium and reduce the infarct size to one quarter to one eighth (1–4). This phenomenon is termed ischemic preconditioning (PC). The PC effect is determined by a combination of the following three factors: 1) duration of PC ischemia, 2) duration of PC reperfusion, and 3) duration of the subsequent ischemia following the PC reperfusion. It has been reported that the PC effect is not induced by a single 2 min ischemia but by two cycles of 2 min ischemia and a single 3, 5 or 10 min ischemia in rabbit hearts (3). It is also reported that the effect is achieved by two or four cycles of 5 min ischemia but not by a single 5 min ischemia in pigs (5) but by a single 5 min ischemia in dogs (2).

Clinically, PC effects have been observed in patients with acute myocardial infarction (AMI) (6–8); that is, a prodromal anginal episode as a PC ischemia before the attack of AMI reduced the infarct size assessed by creatine phosphokinase production and regional wall motion. On the

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Abbreviations and Acronyms

AMI	=	acute myocardial infarction
ANOVA	=	analysis of variance
ISDN	=	isosorbide dinitrate
LAD	=	left anterior descending artery
NC	=	nicorandil
PC	=	preconditioning
PTCA	=	percutaneous transluminal coronary angioplasty

other hand, PC effects have also been observed during coronary occlusions induced by percutaneous transluminal coronary angioplasty (PTCA) (9). However, the results are controversial. That is, some studies reported that 90 and 120 s of occlusion of the left anterior descending coronary artery during the first inflation were effective in reducing the ST segment level during the second inflation (9,10), but others reported that 120 s balloon inflation was not effective (11). We thought that a part of the discrepancy could be explained by the difference in the duration of the PC ischemia. Therefore, it is important to focus on the duration of the PC ischemia in humans.

Several possible mechanisms by which PC protects the heart have been reported. These include adenosine (12,13), noradrenaline (14), bradykinin (15), free radicals (16), the activation of protein kinase C (17) and the opening of KATP channels (18). Among these, the opening of KATP channels has recently been thought to be the end-effector of many signal transduction systems related to the PC mechanism. Therefore, KATP channel openers may be beneficial in protecting the heart against ischemic injury. Nicorandil (NC, N-[2-hydroxyethyl] nicotinamide nitrate), a KATP channel opener with a nitrate-like effect, is currently used clinically as an antianginal drug and is reported to reduce myocardial infarct size in rabbits without collateral circulation (19). Therefore, we hypothesized that NC has a PC-mimic effect on human hearts predisposed to ischemia.

The purpose of this study was to clarify: 1) the optimal duration of the PC ischemia, and 2) the protective effect of NC and its mechanism, using a PTCA model in humans.

METHODS

Subjects. The subjects in this study were composed of forty-six patients with stable angina who satisfied the following criteria: 1) a de novo single lesion with organic stenosis in the proximal left anterior descending artery (LAD), 2) stenosis severity ranging from 75% to 90% according to the American Heart Association classification, 3) the length of the lesions was less than 20 mm. The following exclusion criteria were used: 1) severe stenosis of 99% or over, 2) lesions of a complicated shape with a major side branch, 3) a history of myocardial infarction, diabetes mellitus or severe hypertension, 4) ST segment abnormalities in the surface ECG, such as atrial fibrillation and bundle branch block, etc. All patients gave written, informed consent to the study. The study protocol was approved by the hospital ethics committee.

Grouping of the patients. Patients were randomly allocated to the following four groups: the duration of first inflation for PC ischemia was 60 s in the PC60 group (n = 12) and 180 s in the PC180 group (n = 12). Instead of producing PC ischemia by balloon inflation, a KATP channel opener, NC 80 μg/kg was intravenously given for 1 min in the NC group (n = 12) and isosorbide dinitrate (ISDN) 40 μg/kg was intravenously given for 1 min in the ISDN group (n = 10). After the first inflation or administration of either drug, subsequent inflation was conducted for 120 s in each group (Fig. 1). The site of the second inflation was exactly the same as that of the first.

PTCA procedure. To exclude the effects of various drugs, all the drugs were withdrawn for a week before the procedure except for the administration of 5,000 U of heparin during PTCA.

Percutaneous transluminal coronary angioplasty was performed via a right femoral arterial puncture under local anesthesia with 1% xylocaine. The patients took a rest for 30 min to eliminate the effect of pain due to the puncture. A 6-F guiding catheter and 0.014 in. guide wire were used for PTCA in all patients. Over-the-wire balloons were used in all cases. During inflation, right and left coronary angiography were performed to evaluate collateral circulation. The right coronary angiography was manually performed via an ipsilateral femoral artery puncture using a 5F diagnostic catheter. For the left coronary angiography, a 6F guiding catheter was used in a manual process. To assess the collateral flow to the ischemic zone, a cineangiogram was obtained during ballooning ischemia 30 s after the initiation of balloon inflation and before balloon deflation, both in the first and second inflations. Blood pressure and heart rate were continuously monitored during the procedure.

Blood sampling. Blood sampling was performed before, 30 s and 5 min after NC administration to obtain the measurement of plasma NC concentration. Nonionic contrast medium was used in all cases.

ECG analysis. Standard 12 surface lead ECG (paper speed; 25 mm/s, calibration; 1 mV = 10 mm) was recorded at baseline and at an interval of 30 s during balloon inflation as shown in Figure 1. The level of ST segment 80 ms after the J point in the lead with the largest deviation (deltaST max), as well as the sum of elevated ST segments in all the leads (sigmaST), were determined from the ECG. Changes in ST segment levels during the first inflation in the PC60 group and PC180 group were used as the control, and the differences in ST segment levels between the control and the second inflation (120 s) in the four groups were compared to evaluate the PC effect.

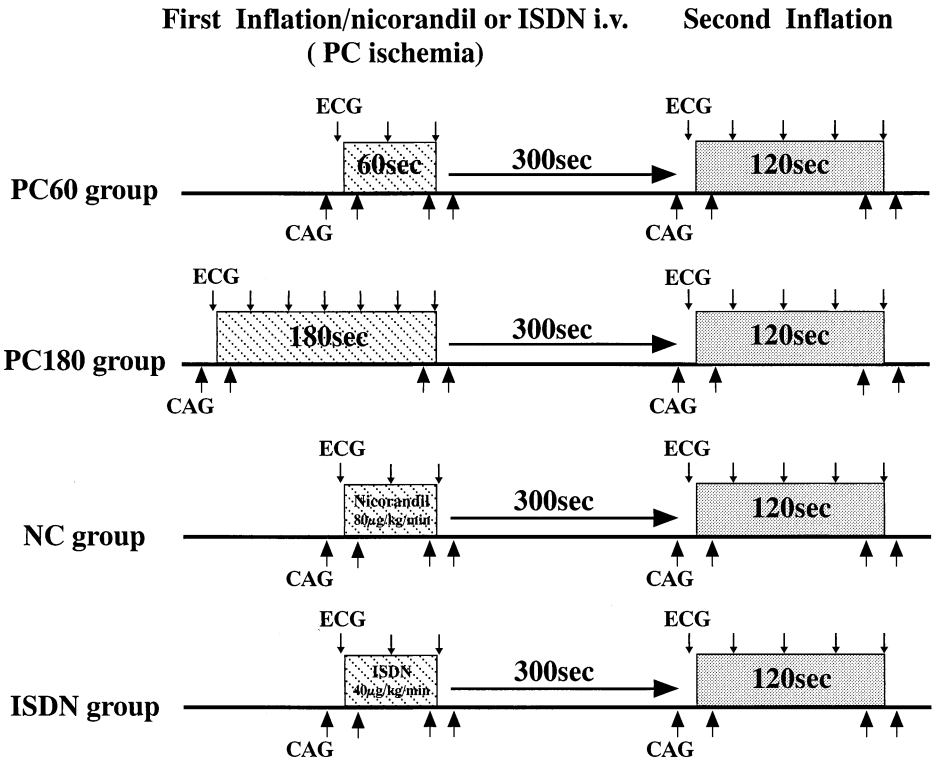

Figure 1. Study protocol. decrease: ECG (body surface 12 lead electrocardiogram); increase: CAG = coronary angiogram.

Statistical analysis. All data are reported as mean ± SD. One-way analysis of variance (ANOVA) was used for the comparison between each group, and if the ANOVA was significant, a modified unpaired *t* test (Fisher's test) was done to assess which group was significantly different. Differences with a value of $p < 0.05$ were considered significant.

RESULTS

Patients' characteristics. Among the four groups comprising the PC60 group, PC180 group, NC group and ISDN group, there were no differences in age or gender. As for the vessel diameter in the lesion before and after PTCA, there was no difference among the four groups. The grade of collateral circulation was evaluated as grade 2 (Rentrop classification) in two cases in each group, and all other cases in each group were grade 0 to 1 (Table 1). In all cases, the collateral circulation remained unchanged during the first and second balloon inflations. There was no difference among the four groups in collateral circulation confirmed by angiography.

Hemodynamic parameters. Changes in hemodynamic parameters such as systolic blood pressure, diastolic blood pressure and heart rate in each group are shown in Figure 2. There was no evidence of significant changes in heart rates in each group. No difference was observed in blood pressure throughout the procedures between the groups with PC ischemia. In the NC group, systolic and diastolic blood pressure significantly decreased until 2 min after the administration of NC. However, this difference was eliminated at the time of ballooning. In the ISDN group, systolic blood pressure significantly decreased until 2 min after the admin-

Table 1. Patient Characteristics

Groups	n	Age (yr)	Gender (M/F)	Collateral Grade (0/1/2/3)	% Diameter	
					pre PTCA	post PTCA
PC60	12	62 ± 8	8/4	8/2/2/0	76 ± 12	20 ± 11
PC180	12	61 ± 10	10/2	9/1/2/0	79 ± 12	19 ± 12
NC	12	62 ± 10	10/2	8/2/2/0	78 ± 11	20 ± 12
ISDN	10	61 ± 9	8/2	7/1/2/0	77 ± 10	19 ± 15

Data are mean ± SD. F = female; ISDN = isosorbide dinitrate 40 μg/kg intravenously given for 1 min; M = male; n = number, NC = nicorandil 80 μg/kg intravenously given for 1 min; PC60 = ischemic preconditioning with 60 s balloon inflation; PC180 = ischemic preconditioning with 180 s balloon inflation; PTCA = percutaneous transluminal coronary angioplasty.

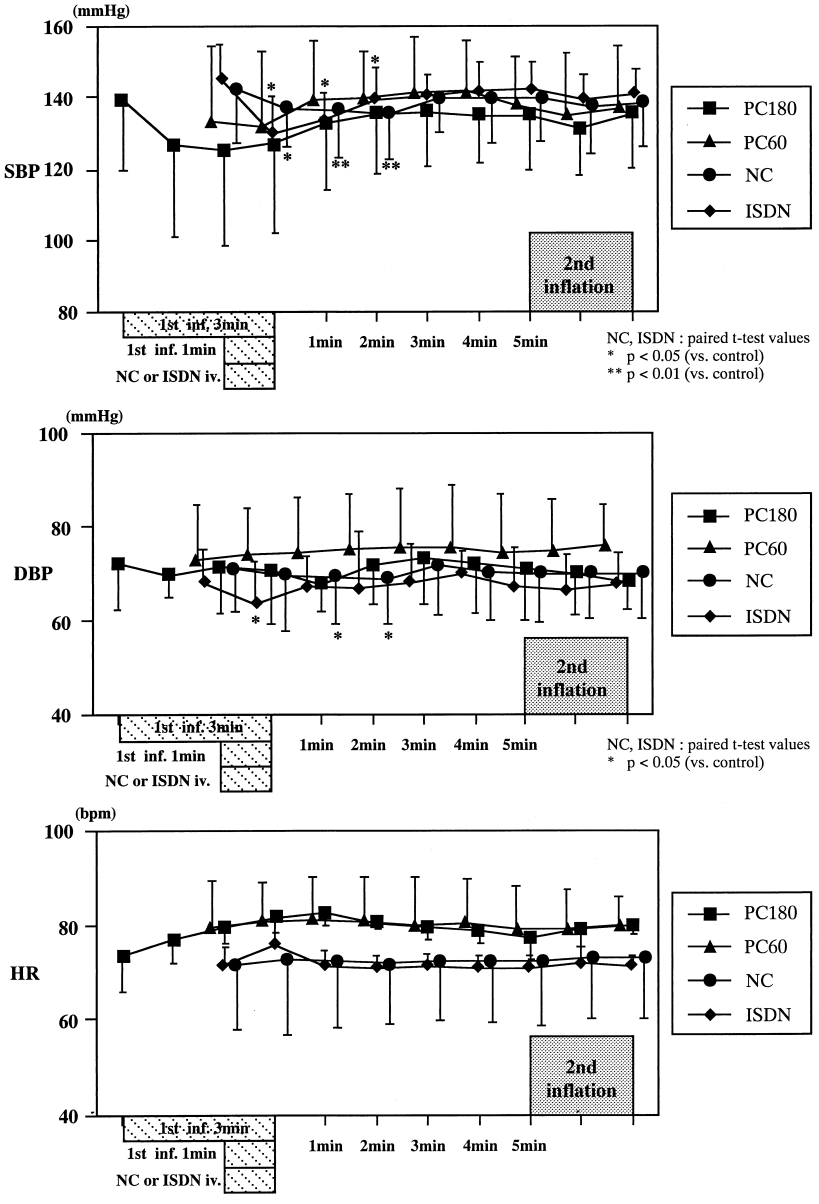

Figure 2. Time course changes in hemodynamic parameters recorded at intervals of 1 min from the control to the end of final inflation. Upper panel: SBP significantly decreased 120 s after the administration of nicorandil or ISDN. Middle panel: DBP significantly decreased 120 s after the administration of nicorandil and significantly decreased only immediately after the administration of ISDN. Lower panel: HR did not alter throughout the experiment in all the groups. DBP = diastolic blood pressure; HR = heart rate; ISDN = isosorbide dinitrate; SBP = systolic blood pressure.

istration. However, diastolic blood pressure significantly decreased immediately after the administration of ISDN.

Changes in ST segment levels (deltaST max, sigmaST) during PC ischemia. The deltaST max of the PC60 group and the PC180 group 30 s after starting the first inflation were 0.28 ± 0.14 and 0.30 ± 0.15 mV, respectively, and there was no difference between the two groups. At 60 s, the values were 0.43 ± 0.19 and 0.40 ± 0.13 mV, respectively, and no difference was observed between the two groups. The PC180 group showed an elevation up to 1.45 ± 0.88 mV at 180 s. The values of the sigmaST in the PC60 group and the PC180 group 30 s after starting the first inflation were 0.88 ± 0.28 and 0.87 ± 0.43 mV, respectively, and there were no differences between the two groups. At 60 s, the values were 1.30 ± 0.37 and 1.31 ± 0.33 mV, respectively, and no difference was observed between the two groups. Accordingly, the deltaST max and sigmaST of the two groups (PC60 group and PC180 group) during the first inflation were used as the control values.

Effect of ischemic PC, ISDN and NC on ST levels. Figure 3 shows deltaST max and sigmaST at 30 s, 60 s, 90 s and 120 s during the second inflation in each group. The ST

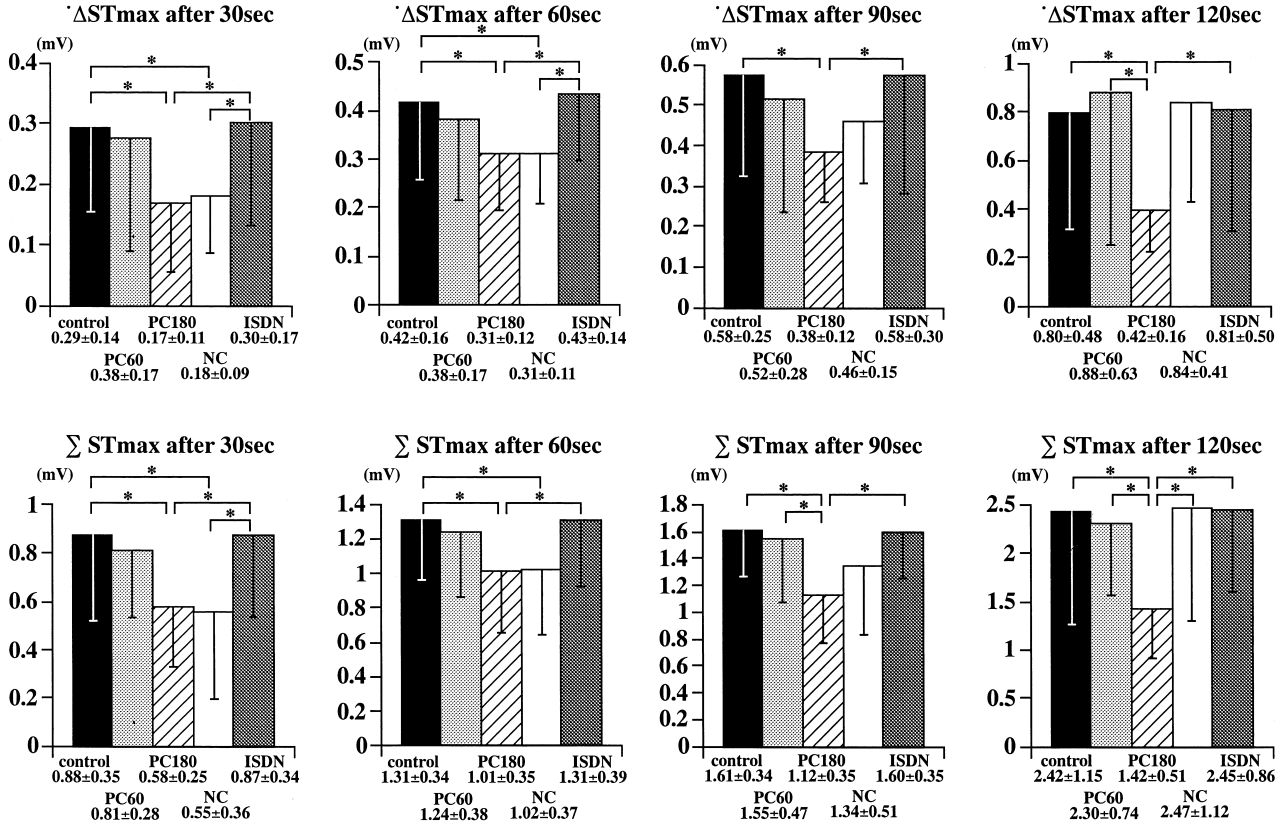

Figure 3. Comparison of deltaST max and sigmaST during the second inflation among control (first inflation of the PC60 and PC180 groups), PC60, PC180, NC and ISDN groups. Significant decreases in ST elevation (deltaST max and sigmaST) in the PC180 group at every time point, and in the NC group at the 30 s and 60 s points after inflation, were observed.

level during the second inflation in the PC60 group showed no significant difference in either deltaST max or sigmaST from the control value at any time point. However, the PC180 group showed significantly lower values in both deltaST max and sigmaST at every time point compared with the control. In the NC group, significant differences in both deltaST max and sigmaST at 30 s and 60 s after balloon inflation were observed compared with the control. However, this difference disappeared at the 90 s and 120 s time points during balloon inflation. In the ISDN group, in contrast, there was no significant difference in either deltaST max or sigmaST compared with the control value at any time point during balloon inflation.

Plasma NC concentration. Plasma NC concentrations were 423 ± 94 and 156 ± 34 ng/ml 30 s and 5 min after administration of 80 μg/kg of NC, respectively.

DISCUSSION

Study limitations. In this study, myocardial ischemia was evaluated by degree of ST level elevation with a 12 lead ECG. The ECG findings associated with myocardial ischemia include various changes in depolarization and repolarization such as Q waves, ST elevation and ST depression, high positive T waves and deep negative T waves. Among these, ST elevation is the most important indicator of ECG findings that indicates ischemia. The ST elevation due to myocardial ischemia is caused when an abnormal injury current passes through the border of the normal region and the ischemic region (20). The degree of ST elevation is also affected by complicated factors such as medication, conduction disturbance and electrolyte disorder other than real ischemia. Therefore, the degree of ST elevation is not a direct and absolute indicator of ischemia, but, from the viewpoint of the membrane potential, reflects ischemic injury indirectly (21).

From our experience, although intracoronary ECG has excellent sensitivity, the subtle positioning may impose tremendous influence on the voltage potential. Therefore, we employed only a body surface ECG, which is easier to handle and more stable than intracoronary ECG. Furthermore, we examined the effects of NC on ST segment levels during PTCA.

When the duration of the PC ischemia is relatively long, such as 180 s, the contribution of collateral circulation should be considered. In this study, angiography for detection of collateral flow was performed twice during each PTCA (30 s after inflation and 30 s after deflation) in the 180 s, 120 s, NC and ISDN groups. The grade of collateral

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circulation was less than 2 in each patient and mostly 0 in each of the four groups. That is, there was no evidence of rich collateral, reflecting the fact that each patient had single vessel disease and the percent diameter stenosis was less than 90% (22). It did not change between the 180 s and 120 s PTCAs in the 180 s group or between the 60 s and 120 s PTCAs in the 120 s group. It was also similar among the 120 s PTCAs of the four groups. These results suggest that collaterals are independent of the differences in ST changes during PTCA in the four groups.

The optimal duration of PC ischemia. Murry et al. (1) reported that PC due to a brief period of ischemia and reperfusion reduced the size of myocardial infarction in dogs. Recently, some clinical studies on PC during PTCA in humans have been reported. However, the data are controversial. As for the duration of PC ischemia, one or two cycles of 90–120 s ischemia were used to induce the PC effect in many studies (9–11). Some reported that a 90 or 120 s first balloon inflation was effective in reducing the level of ST segment elevation during the second inflation (9,10), and others reported that a 120 s balloon inflation was not effective (11). In animal models, 180 s ischemia, but not 120 s ischemia, induces a PC effect (23). Therefore, questions are raised for humans. Is PC ineffective if the duration is shorter than 90 s? Is PC more effective if the duration is longer than 120 s? In this study, focusing on this point, we evaluated the difference in the PC effects between two different durations of PC ischemia: 60 s and 180 s. Our results clearly demonstrated that PC ischemia of 180 s, but not of 60 s, followed by 5 min PC reperfusion produced a PC effect without recruitment of collateral flow. Therefore, the duration of PC ischemia is important in humans as well as animal models. In addition, this may explain the previous discrepancy in the PC effect when using a PTCA model in humans.

KATP channel and the mechanism of PC. There are many candidates for mechanisms of PC such as adenosine, noradrenaline, bradykinin and free radicals, all of which activate protein kinase C and then induce the PC effect. Recently, it has been reported that the activation of protein kinase C opens the KATP channels (24) and the opening of mitochondrial KATP channels is currently thought to be the end-effector of many signal transduction systems related to the PC mechanism (25). Therefore, it is thought that KATP channel openers are also effective in protecting against human ischemic injury.

Dosage of NC and ISDN. Motohara et al. (26) reported that plasma concentrations of NC 3 min after IV administration at doses of 50 μg/kg were 102 ± 34 ng/ml in humans. Reduction in afterload following the injection disappeared 2 minutes later. In this study, reduction of afterload after IV dose (80 μg/kg) also disappeared 2 minutes later. We administered 40 μg/kg of ISDN intravenously because this dose has a similar hypotensive effect as 80 μg/kg of nicorandil (27). In fact, reduction of afterload after the ISDN injection also disappeared 2 min later. The effect on heart rate was not seen in either NC or ISDN. Thus, blood pressure and heart rate during PTCA were similar between the NC and ISDN groups.

Mechanism of NC action. Nicorandil, which is currently used clinically as an antianginal drug, is a hybrid nitrate with KATP channel opening effects (28) and has been reported to reduce myocardial infarct size in animal models (19,29). In the present human study, pretreatment with NC suppressed the elevation in ST segment levels due to a brief period of ischemia, suggesting that this drug has a pharmacological PC effect in humans. It is necessary to clarify whether the PC effect of NC is due to the opening of KATP channels or nitrate-like effect. Auchampach et al. (30) conducted an experiment in dogs and reported that NC attenuated myocardial dysfunction associated with transient ischemia and that this effect was inhibited by glibemclamide, a KATP channel blocker, indicating the involvement of the KATP channel in the effect of NC. However, glibenclamide is only prescribed for diabetic patients and its use is not allowed for nondiabetic patients. Therefore, in this study, the effect of ISDN was compared with that of NC. No PC effect was seen in the ISDN group. In addition, blood pressure, heart rate and collaterals during ischemia were similar between the NC and ISDN groups. Therefore, it is suggested that the pharmacological PC effect of NC was not due to depression of afterload, collaterals or a nitrate-like effect but to the opening of KATP channels.

Conclusions. There is an optimal duration of PC ischemia in humans as well as animal models and it is not 60 s, but 180 s in humans. Nicoramdil has a pharmacological PC effect by opening KATP channels.

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